IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,

Plaintiff,

v.

MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS INC.,

Defendants.

C.A. No. 19-cv-2017 (RGA)(SRF)
(Consolidated)

[redacted]

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MSN'S OPPOSITION TO PLAINTIFF'S MOTION TO EXCLUDE THE OBVIOUSNESS OPINIONS OF SALVATORE LEPORE AND JONATHAN STEED AND ANY REFERENCE TO THEM BY OTHER EXPERTS

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While Exelixis' Motion is postured as a *Daubert* motion, in reality it is a thinly veiled attack on the ultimate obviousness opinions reached by MSN's experts. Exelixis does not challenge the credentials or expertise of Drs. Lepore and Steed—both highly qualified experts in their respective fields. Nor does Exelixis dispute their scientific methods or the application of those methods to the facts of this case to arrive at their opinions (as required under *Daubert*). In other words, Exelixis is not challenging the reliability of the specific opinions offered by Drs. Lepore and Steed, but rather essentially seeks summary judgment on the overall evidentiary sufficiency of MSN's obviousness claims. Such arguments find no basis under *Daubert* and should be summarily rejected.

Exelixis feigns "surprise" that they are not "fairly on notice" of MSN's theory of obviousness. (Exelixis' Opening Br. in Supp. of Its Mot. To Exclude the Obviousness Opinions of Dr. Lepore and Dr. Steed and Any Reference to Them By Other Experts, 2022, D.I. 258 ("Br.") at 10.) That claim is difficult to understand given that MSN's theories are thoroughly spelled out chapter and verse in Dr. Lepore's and Dr. Steed's Opening Reports, which span 93 pages and 100 pages, respectively. Exelixis' experts also clearly understood the obviousness opinions to which they were responding when they submitted their own voluminous reports in rebuttal. Likewise, Exelixis' counsel spent six to seven hours deposing each expert without any apparent difficulty understanding the scope of their opinions.

Exelixis ignores Dr. Lepore's and Dr. Steed's actual substantive analysis by claiming that "neither expert identifies any specific combination of references," but rather "offer a menu of combinations" that lead to "millions if not billions of alternative options." Br. at 1. But Exelixis' hyperbole misrepresents Drs. Lepore's and Steed's opinions and attempts to fault them for submitting thorough reports that faithfully adhere to the law of obviousness—which requires them

to detail the scope and content of the prior art and identify the lack of differences between the prior art and the asserted claims. Further, Exelixis' claim that identifying specific combinations is a "prerequisite to demonstrating obviousness" misstates the law and has no bearing on the actual inquiries that the Court must undertake. (Br. at 4.) The Supreme Court in *KSR* set out "'an expansive and flexible approach' to 'the question of obviousness.'" *Uber Techs., Inc. v. X One, Inc.*, 957 F.3d 1334, 1338–39 (Fed. Cir. 2020) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)). Indeed, where, as here, the "entire body of prior art"—or an "evidentiary cornucopia"—renders a patent claim obvious, a trier of fact can fairly rely on "any combination of these references in reaching its obviousness verdict." *Rothman v. Target Corp.*, 556 F.3d 1310, 1320-21 (Fed. Cir. 2009). The fact there are many combinations that each render the disputed claims obvious is not a basis to exclude their opinions, but is rather strong evidence that the claim elements were well-known in the prior art.

Finally, Exelixis ignores that "*Daubert* considerations are less pressing in the context of a bench trial." *LG Display Co., Ltd. v. AU Optronics Corp.*, 265 F.R.D. 199, 207 (D. Del. 2010). Because this Court will be able to place the appropriate weight on the various opinions and evidence presented at trial, there is no reason to exclude expert opinions before hearing the testimony at trial, and especially not from MSN's distinguished experts on what will be central issues in the case. Dr. Lepore's and Dr. Steed's analyses are carefully considered, thoroughly supported, and faithfully follow the Supreme Court's articulation of the obviousness inquiry. Their expertise and scientific methods are beyond reproach and their credentials are not even challenged by Exelixis (whose own experts consider Dr. Lepore "a respected researcher" and Dr. Steed as

having "a good reputation as a researcher").[1] Exelixis' motion fails the principles of *Daubert* and should be denied.

I. BACKGROUND

Exelixis, Inc. is pursuing claims against MSN in this Hatch-Waxman suit for alleged infringement of U.S. Patent Nos. 7,579,473 ("the '473 patent"), 8,497,284 ("the '284 patent"), and 8,877,776 ("the '776 patent"). The '473 patent claims the compound cabozantinib, including its pharmaceutically acceptable salts; the '284 patent claims a method of treatment using cabozantinib or its pharmaceutically acceptable salts; and the '776 patent claims a polymorphic form of a specific pharmaceutical salt of cabozantinib. Yet the cabozantinib compound is formed through a simple modification to a lead compound known in the prior art. And the polymorph claimed in the '776 patent is formed through a routine method of preparing a pharmaceutical salt. Dr. Lepore addresses obviousness issues with respect to the '473 and '284 patents, and Dr. Steed addresses the '776 patent. Drs. Lepore and Steed opine that Exelixis' asserted claims were not inventive or novel but rather the obvious combination of familiar elements according to known methods that do no more than yield predictable results.

II. LEGAL STANDARD

Exelixis' *Daubert* challenge is founded on a misunderstanding of the law of obviousness. "Obviousness is a question of law based on underlying factual determinations including: (1) the level of ordinary skill in the pertinent art, (2) the scope and content of the prior art, (3) the differences between the prior art and the claims at issue, and (4) secondary considerations of non-obviousness such as commercial success, long-felt but unsolved needs, failure of others, etc." *Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir.

[1] Ex. A ("MacMillan Tr.") at 15:21-23; Ex. B. ("Trout Tr.") at 74:13-16.

2019) (quoting *KSR*, 550 U.S. at 406) (internal quotation marks omitted). The Supreme Court has specifically rejected any "[r]igid preventative rules that deny factfinders recourse to common sense," urging instead "'an expansive and flexible approach' to 'the question of obviousness' under 35 U.S.C. § 103." *Uber Techs., Inc. v. X One, Inc*., 957 F.3d 1334, 1338–39 (Fed. Cir. 2020) (quoting *KSR*, 550 U.S. at 415, 421). The "motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather may be found in any number of sources, including common knowledge, ***the prior art as a whole***, or the nature of the problem itself." *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1362 (Fed. Cir. 2007) (citing *DyStar Textilfarben GmbH v. C.H. Patrick Co.,* 464 F.3d 1356, 1360 (Fed. Cir. 2006) (emphasis added)).

Exelixis also fails to recognize that "[i]t is simply less critical to pre-screen expert testimony in the bench trial setting, since the court can simply disregard expert evidence that it regards as unreliable, irrelevant, or unhelpful." *APEX Fin. Options, LLC v. Gilbertson*, 2022 WL 613347, *3 (D. Del. March 1, 2022) (collecting cases); *see also Seaboard Lumber Co. v. United States*, 308 F.3d 1283, 1302 (Fed. Cir. 2002) ("[T]hese [*Daubert*] concerns are of lesser import in a bench trial."). Under *Daubert*, the "ultimate touchstone is helpfulness to the trier of fact" and "[a] judge frequently should find an expert's methodology helpful even when the judge thinks that the expert's technique has flaws sufficient to render the conclusions inaccurate." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 744–45 (3d Cir. 1994).

III. ARGUMENT

Exelixis' motion claims that "Dr. Lepore's and Dr. Steed's failure to disclose any specific obviousness combinations" will cause Exelixis to be "prejudiced," because Exelixis and its experts have purportedly "been unable to prepare any response." Br. at 10. As a preliminary matter, Exelixis' motion fails because Dr. Lepore's and Dr. Steed's reports disclose specific combinations

as explained below. These specific combinations were made explicit in MSN's supplemental invalidity contentions served over six months ago and are fully detailed in their opening expert reports, which were served last October. Yet, Exelixis first raised its purported concerns with the expert disclosures—under the guise of a *Daubert* challenge—during a meet and confer on March 9, 2022. But efficient case management, now incorporated in this Court's Form Scheduling Order for Patent Cases, requires a party to promptly raise any such concerns: "[i]f any party believes that an expert report does not comply with the rules relating to timely disclosure or exceeds the scope of what is permitted in that expert report, the complaining party must notify the offending party within one week of the submission of the expert report." (*See* Judge Richard Andrews Rule 16 Scheduling Order – Patent (Rev. 12/19).) Here, Exelixis did not raise its concern until nearly five months after the submission of Drs. Lepore's and Steed's Opening Reports. Notwithstanding its untimeliness and ill-fit as a *Daubert* motion, Exelixis' motion further fails because Dr. Lepore's and Dr. Steed's opinions are fully disclosed, straightforward and powerfully supported by the prior art.

A. Dr. Lepore's and Dr. Steed's Obviousness Analyses Comply with *KSR*.

Dr. Lepore's and Dr. Steed's Reports detail "(1) the level of ordinary skill in the pertinent art, (2) the scope and content of the prior art, (3) the differences between the prior art and the claims at issue, and (4) secondary considerations of non-obviousness." *Novartis,* 923 F.3d at 1059 (quoting *KSR,* 550 U.S. at 406). Exelixis, however, paints a distorted picture of those opinions and claims that "neither expert has identified any specific combination of references, any motivation to combine any specific disclosure within a combination of references, or any basis for a POSA to have had a reasonable expectation of achieving the claimed inventions." (Br. at 4.) The reports themselves show otherwise.

Dr. Lepore's Opening Invalidity Report begins with a description of the hypothetical person of ordinary skill in the art ("POSA"). (Ex. C, Opening Expert Report of Dr. Salvatore Lepore Regarding Invalidity of U.S. Patent Nos. 7,579,473 and 8,497,284 ("Lepore Report") at ¶¶ 29-31.) Dr. Lepore then explains the relevant state of the art at the time of the alleged inventions, including a technology tutorial on motivating attributes considered during small molecule drug design (*id*. at ¶¶ 68-76), the importance of oral bioavailability of a drug candidate (*id*. at ¶¶ 77-86), and that structurally similar compounds to cabozantinib were known to be useful for treating cancers (*id*. at ¶¶ 87-102). Dr. Lepore continues his analysis by identifying and describing the scope and content of the prior art, including the primary Kirin references (*id*. at ¶¶ 105-120), publications teaching how to select a lead compound for drug development (*id*. at ¶¶ 121-143), references teaching how to modify a lead compound (*id*. at ¶¶ 144-192), and other prior art related to developing pharmaceutically acceptable salts (*id*. at ¶¶ 193-202). Dr. Lepore then describes in exacting detail why a POSA would have been motivated to combine the cited references to select the compound disclosed by Kirin as a lead compound (*id*. at ¶¶ 208-233) and to modify that lead compound to create an improved inhibitor (*id*. at ¶¶ 240-256) that is more metabolically stable (*id*. at ¶¶ 234-239), among other reasons.

In a similarly comprehensive fashion, Dr. Steed's Opening Invalidity Report begins with a description of a POSA. (Ex. D, Opening Expert Report of Jonathan Steed, Ph.D., Regarding Invalidity of the Asserted Claims of U.S. Patent Nos. 8,877,776 ("Steed Report") at ¶¶ 26-29). Dr. Steed then describes the relevant state of the art at the time of the alleged inventions, including discussions of pharmaceutical salts and their synthesis and selection (*id*. at ¶¶ 45-71) and a description of polymorphism with respect to pharmaceutical salts, including the selection and identification of polymorphs (*id*. at ¶¶ 72-111). Dr. Steed continues his analysis by identifying and

describing the scope and content of the prior art, including the primary references that disclose pharmaceutically acceptable salts of cabozantinib (*id*. at ¶¶ 126-138), publications teaching how to screen for and select pharmaceutical salts (*id*. at ¶¶ 139-173), and prior art teaching how to screen for and select polymorphs of pharmaceutical salts (*id*. at ¶¶ 174-214). Dr. Steed then details why a POSA would have been motivated to combine these references to prepare a pharmaceutical salt of cabozantinib (*id*. at ¶¶ 219-232), to select the (L)-malate salt (*id*. at ¶¶ 233-243), and why that decision would have reasonably led to the formation of the claimed Form N-2 polymorph (*id*. at ¶¶ 244-262), among other reasons.

Exelixis may disagree with the ultimate obviousness opinions of Dr. Lepore and Dr. Steed, but Exelixis' incredulous assertion that their "opinions do not adequately disclose MSN's invalidity positions" and "should be excluded in their entirety" so that Exelixis is not "surprise[d]" at trial entirely lacks merit. Br. at 10.

B. Both Experts Identified Specific Combinations to Illustrate the Lack of Differences Between the Prior Art and the Claims.

As discussed above, Dr. Lepore's and Dr. Steed's obviousness analyses comply with Rule 26's requirement that an expert report provide "a complete statement of all opinions the witness will express and the basis and reasons for them" (Fed. R. Civ. P. 26(A)(2)(B)(i))). Critically, neither Dr. Lepore nor Dr. Steed will present at trial any opinions that were not disclosed in their reports (thus mooting Exelixis' request to preclude them from providing testimony "not discussed in their expert reports."). (*See* Br. at 10-11.)

Exelixis claims, however, that they failed to "[i]dentify a specific combination of references [which] is a prerequisite to demonstrating obviousness." (Br. at 4.) But the Supreme Court has specifically rejected any stringent requirement for analyzing obviousness, urging instead "'an expansive and flexible approach' to 'the question of obviousness' under 35 U.S.C. § 103."

Uber Techs., Inc. v. X One, Inc., 957 F.3d 1334, 1338–39 (Fed. Cir. 2020) (quoting *KSR*, 550 U.S. at 415). In *KSR*, the Supreme Court stated that the obviousness of a claim need not arise from a single prior art reference; it can be shown by the "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art." *KSR*, 550 U.S. at 418.

Exelixis claims to be "prejudiced" because Exelixis and its experts have purportedly "been unable to prepare any response" to "Dr. Lepore's and Dr. Steed's failure to disclose any specific obviousness combinations." (Br. at 10.) But this claim rings hollow when the voluminous and point-by-point Rebuttal Reports submitted by Exelixis' experts Dr. MacMillan and Dr. Trout are considered, totaling 244 pages and 122 pages, respectively. While MSN certainly disputes Dr. MacMillan's and Dr. Trout's conclusions, even a cursory review of the table of contents of their Rebuttal Reports shows that they fully understood the obviousness theories set forth in MSN's experts' reports. For instance, Dr. MacMillan has a section of his Report titled "Claims 1-7 of the '473 Patent Would Not Have Been Obvious Over the Lepore Combinations," which contains subsections closely tracking and responding to Dr. Lepore's lead compound analysis. (Ex. E at iv-v.) Likewise, Dr. Trout's report contains a section titled "The Inventions of the Asserted Claims Are Not Obvious Over the References Cited by Dr. Steed," which contains subsections that mirror the motivations described in Dr. Steed's obviousness analysis. (Ex. F at iv-v.)

Moreover, when deposing Dr. Lepore, Exelixis' counsel asked detailed questions regarding the specific combinations (Ex. G ("Lepore Tr.") 11:18-13:2), the specific motivations to combine (*see, e.g., id*. at 122:18-24 ("It is your opinion that a POSA would have been motivated to pursue c-Met tyrosine kinase inhibitors …?"); 199:12-16), and the specific reasonable expectations of

success (*see, e.g., id*. at 248:21-249:3) described in his report. Likewise, when deposing Dr. Steed, Exelixis' counsel clearly understood his theories regarding specific combinations (Ex. H ("Steed Rough Tr.") 25:24-27:10), the specific motivations to combine (*see, e.g., id*. at 2:24-3:1 ("Your opinion is that a person would have been motivated to improve the solub[ility] of the free base of cabozantinib, do I have that right?"); 4:22-24; 19:21-24), and the specific reasonable expectations of success (*see, e.g., id*. at 138:3-8).

The reason Dr. MacMillan and Dr. Trout were able to prepare responses in their own Rebuttal Reports and that Exelixis' counsel was able to spend nearly seven hours deposing each expert is because Dr. Lepore and Dr. Steed clearly disclosed their opinions.

1. Dr. Lepore Disclosed Specific Combinations.

As Exelixis concedes, Dr. Lepore disclosed his specific combinations at paragraph 204 of his Opening Report. *See* Br. at 5-6 (citing Lepore Opening Report ¶ 204). Exelixis claims this "large menu of combinations" discloses "15 million potential obviousness combinations" (Br. at 5), but that claim both ignores that a POSA is presumed to be familiar with all relevant and publicly available prior art and also mischaracterizes the law. In a lead compound analysis, to "show that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention," the Federal Circuit has held that "[i]n keeping with the flexible nature of the obviousness inquiry, the requisite motivation to modify can come from *any number of sources*." *Procter & Gamble Co. v. Teva Pharms. USA, Inc*., 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation marks omitted) (emphasis added). Further, "[i]t is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship ... to create an expectation,' in light of *the totality of the prior art*, that the new compound will have 'similar properties' to the old." *Bristol–Myers SquibbCo. v. Teva Pharms. USA, Inc*., 752 F.3d 967, 977

(Fed. Cir. 2014) (citing *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc*., 678 F.3d 1280, 1293 (Fed. Cir. 2012)) (emphasis added).

Dr. Lepore's analysis is actually very simple, and convincingly shows that the claimed cabozantinib compound would have been obvious because a POSA would have been motivated to select the lead compound described in the Kirin reference for modification, and a POSA would have had several motivations to make the single modification of that compound to include a spiro-cyclopropyl ring. Dr. Lepore discloses that a POSA would have selected Example 5 of Kirin as a lead compound and cites to two groups of references supporting a POSA's motivation to have selected Example 5—"the prior art regarding c-Met's role in various Cancers, i.e.: Ueki, Maulik, Shawver, or Traxler (discussed in the Mega Opening Report, Section VIII.A)" and "the prior art related to selecting a lead compound, i.e.: the '746 patent, Onderwater 1998, Onderwater 1999, Lipinski, Ghose, or Egan." (Lepore Opening Report ¶ 204.) Then, Dr. Lepore cites to another group of references that individually and collectively provide motivational reasons to modify that compound to include a spiro-cyclopropyl ring—"the prior art related to modifying the lead compound, i.e.: Williams, the '992 patent, Nes, McMorris, Kelner 1995, Kelner 2000, the '746 patent, Salaün, Wessjohann, the '410 patent, Fry, Allen, NCT '830, or NCT '051." *Id*. The Federal Circuit has affirmed findings of obviousness where "the totality of the prior art" supports that a modification would have been a minor one, as described in Dr. Lepore's analysis. *Bristol-Myers Squibb*, 752 F.3d at 975 (discussing multiple references and finding that "the substitution was an obvious modification in light of the prior art").

Dr. MacMillan also had no trouble responding to the combinations disclosed by Dr. Lepore. For instance, Dr. MacMillan discussed whether a POSA would have been motivated to look to the teachings of the Lipinski prior art reference when seeking to modify Example 5 of Kirin. (Ex. E at

¶ 373.) Similarly, Dr. MacMillan also discusses whether a POSA would have been motivated to combine Example 5 of Kirin with references including Salaün, the '992 patent, the '746 patent, and the '410 patent. (*Id*. at ¶ 380.) These are only a few examples in Dr. MacMillan's report that demonstrate he understood the specific combinations and organization disclosed by Dr. Lepore.

2. Dr. Steed Disclosed Specific Combinations.

Similarly, Exelixis concedes that Dr. Steed also disclosed specific combinations in his report. (*See* Br. at 7-8 (citing Steed Opening Report ¶ 216).) Exelixis claims this "large menu of combinations" discloses "60 billion potential obviousness combinations" (Br. at 7), but that claim again both ignores that a POSA is presumed to be familiar with all relevant and publicly available prior art and mischaracterizes the law. It also misconstrues the chart Dr. Steed provided to help organize and disclose his opinions by describing the relevant prior art in three different categories. For an obviousness analysis related to the formation of a pharmaceutical salt, like the one performed by Dr. Steed, a "motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *Pfizer, Inc. v. Apotex*, *Inc*., 480 F.3d 1348, 1362 (Fed. Cir. 2007) (citing *DyStar Textilfarben GmbH v. C.H. Patrick Co.,* 464 F.3d 1356, 1360 (Fed. Cir. 2006)). When determining whether to form a pharmaceutical salt, an expert may rely on "chemical characteristics as reported in several [] publications" and "patents" "taken together" to "provide ample motivation." *Id*. at 1363.

Dr. Steed's analysis follows this simple framework and relies on several references "taken together." *Id*. Dr. Steed relies on a small group of references to describe why a POSA would have found it obvious to prepare a pharmaceutical composition comprising cabozantinib—the '564 patent, the '928 application, and the '140 publication, each of which makes similar disclosures.

(Steed Opening Report ¶ 216.) Then Dr. Steed cites to a group of publications that individually and collectively teach the benefits of forming a pharmaceutical salt, and in particular, render obvious forming and selecting an L-malate salt for development—Bighley, Berge, Paulekuhn, '905 patent, '198 patent, '338 patent, '835 patent, '621 patent, '107 patent, '307 patent, '070 patent, '407 patent, '483 patent, Tong, and Fieser. (*Id*.) Finally, Dr. Steed relies on another group of references to show that the specific polymorphic form claimed in the '776 patent would have been an obvious result of routine screening for an L-malate salt, or alternatively, that it would have been obvious to screen for additional polymorphic forms to obtain the claimed form—Remington's 2000, Shekunov, Yu, Caira, Hornedo, Gu, Vippagunta, Byrn, Haleblian 1969, Haleblian 1975, Threlfall, McCrone, Guillory, Brittain, Desiraju, FDA Guideline, ICH Guideline. (*Id*.) Like Dr. Steed's analysis, the Federal Circuit has found in the context of analyzing the obviousness of a pharmaceutical salt "that several publications … were prior art … and pertinent to the problem the inventors sought to overcome" and that "here, all claim limitations [we]re found in a number of prior art references." *Pfizer*, 480 F.3d at 1361.

Dr. Trout also had no difficulty responding to the combinations disclosed by Dr. Steed. For instance, Dr. Trout discusses whether a POSA would have been motivated to combine the '928 application, which discloses and claims cabozantinib and its pharmaceutical salts, with Fieser (Ex. F at ¶ 243), Remington's 2000 and Berge (*id*. at ¶ 249), and Tong (*id*. at ¶ 261). Again, these are only a few examples in Dr. Trout's report that demonstrate he understood the specific combinations and organization disclosed by Dr. Steed.

3. Multiple Combinations of Prior Art Render the Claims Obvious.

Exelixis challenges Drs. Lepore's and Steed's opinions on the basis that *multiple* combinations render the asserted claims obvious. But Drs. Lepore and Steed cannot be faulted for performing the analysis required under *KSR*—to detail the scope and content of the prior art as

well as the lack of the differences between the prior art and the claims. *KSR,* 550 U.S. at 406. That there are *many* combinations that each render the claims obvious is certainly not a basis to exclude their opinions but is rather further evidence that the claim elements were well-known in the prior art and described in similar fashion in multiple references. Because the "entire body of prior art"—or an "evidentiary cornucopia"—renders these claims obvious, the trier of fact can fairly rely on "any combination of these references in reaching its obviousness verdict." *Rothman*, 556 F.3d 1310, 1320-21 (Fed. Cir. 2009).

C. Dr. Lepore and Dr. Steed Disclosed Motivations to Combine Specific Teachings.

Exelixis further wrongly claims that "Drs. Steed and Lepore have also failed to identify any motivation to combine" the disclosed prior art references and that they "nowhere provided reasons that a POSA would have been motivated to combine any specific disclosures." (Br. at 9.) This assertion, however, grossly mischaracterizes their reports, as entire sections are dedicated to specific motivations to combine references.

Dr. Lepore repeatedly emphasizes certain motivations such as the need for sufficient bioavailability, the desirability of an irreversible inhibitor, and the benefits of improved metabolic stability in modifying a lead compound. For example, Dr. Lepore details why bioavailability is a critical property considered during drug development and explains that a POSA would have looked to Lipinski's rule of five to predict the bioavailability of the lead compound disclosed in Kirin. (*See*, *e.g.*, Lepore Report at ¶¶ 228-229, 238.) As another example, Dr. Lepore cites to specific references such as Fry, Allen, NCT '830; NCT '051, and Traxler that individually and collectively would have motivated a POSA to prepare an irreversible inhibitor (*See*, *e.g.*, Lepore Report at ¶¶ 255-256) while also discussing specific disclosures, such as Salaün, the '992 patent, the '746 patent, the '410 patent, Wessjohann, Kelner 1995, and McMorris that individually and collectively

would have motivated modifying the lead compound to include a spiro-cyclopropyl group, including to form a more metabolically stable compound. (*See*, *e.g.*, Lepore Report at ¶¶ 234-239.)

Likewise, Dr. Steed discloses motivations for forming the claimed L-malate salt of cabozantinib, including the desire to increase aqueous solubility for formulation in an oral dosage form, the benefits of performing a salt screen to methodically synthesize and analyze pharmaceutical salts and their polymorphic forms, and motivations to select the L-malate salt. For instance, Dr. Steed relies on references including the '928 application, Bighley, Remington's 2000, Fieser, and Shekunov for the motivation to increase cabozantinib's aqueous solubility for formulation in an oral dosage form, which is a preferred route of administration, by forming a pharmaceutical salt. (*See*, *e.g.*, Lepore Report at ¶¶ 223-225.) Dr. Steed cites to Tong, 1987 FDA Guidelines, ICH Guidelines, Caira, Vippagunta, and Guillory to describe methods of screening for pharmaceutical salts and their polymorphic forms that are routinely successfully used in the industry. (*See*, *e.g.*, *id*. at ¶¶ 235, 257-260.) Further, Dr. Steed explains that multiple references, including Bighley, Paulekuhn, the '198 patent, and the '905 patent, would have individually and collectively motivated a POSA to select the L-malate salt because of its accepted use in the industry, its ability to increase solubility, and its lack of known toxicity issues. (*See*, *e.g.*, *id*. at ¶¶ 237-238, 240.)

The Federal Circuit has time and again held analysis of this sort sufficient to show a motivation to combine prior art references, which in turn may support an obviousness finding. *See, e.g., In re Ethicon, Inc*., 844 F.3d at 1350 ("The normal desire of artisans to improve upon what is already generally known can provide the motivation to [combine prior art references]."); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co*., 464 F.3d 1356, 1366 (Fed. Cir. 2006) ("[A] motivation to combine need not be found in the prior art references themselves, but

rather may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved."). Further, because "an expert is not the only source for evidence that it would be obvious for one skilled in the art to combine references to reach the claimed method," this basis is not a sufficient reason to exclude their reports in their entirety. *Innogenetics, N.V. v. Abbott Lab'ys*, 512 F.3d 1363, 1374 (Fed. Cir. 2008).

D. Dr. Lepore and Dr. Steed Provide Rationales Why a POSA Would Have Had a Reasonable Expectation of Success.

Exelixis contends that "neither expert has identified … any basis for a POSA to have had a reasonable expectation of achieving the claimed inventions." (Br. at 4.) But in substance, Exelixis merely disagrees with whether the expectation would have been reasonable, not whether a basis was disclosed. When evaluating whether there would have been a reasonable expectation of success in combining prior art references, the "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer,* 480 F.3d at 1364 (citing *In re Corkill,* 771 F.2d 1496, 1500 (Fed. Cir. 1985)) ("a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt—including those specifically listed in the '909 patent itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.").

Dr. Lepore clearly discloses that it would have been reasonable to expect that modifying Example 5 of Kirin would have been successful due to the numerous other examples in the art including compounds disclosed in the Kirin reference, as well as inhibitors with a spirocyclopropyl ring, including Salaün, the '992 patent, the '746 patent, the '410 patent, Wessjohann, Kelner 1995, Kelner 2000, and McMorris. (Lepore Report at ¶¶ 242-253.) Likewise, Dr. Steed explains that a

POSA would have had a reasonable expectation of forming an L-malate salt based on the wide-spread use of L-malate as a pharmaceutical salt, as taught by Bighley, Paulekuhn, the '198 patent, and the '905 patent. (*See, e.g.*, *id*. at ¶¶ 237-238, 240.) Further, Dr. Steed describes why a POSA would have had a reasonable expectation of success in obtaining the claimed form because numerous references, such as Tong, 1987 FDA Guidelines, ICH Guidelines, Caira, Vippagunta, and Guillory, all describe successful screening methods for pharmaceutical salts and their polymorphs. (*See*, *e.g.*, *id*. at ¶¶ 235, 257-260.) Exelixis' arguments amount to nothing more than a disagreement with MSN's experts' ultimate conclusions.

E. Case Law Cited by Exelixis Is Inapplicable or Readily Distinguishable.

The thorough and fully disclosed opinions submitted by Drs. Lepore and Steed are easily distinguished from the opinions at issue in the authority Exelixis relies upon. For instance, Exelixis cites to *ProBatter Sports, LLC v. Sports Tutor, Inc.*, where the court criticized defendant's reference to "a slew of references in ten separate obviousness combinations, some of which combined as many as five different references." 680 F. App'x 972, 975 (Fed. Cir. 2017). But in that case, the defendant "merely cited, without explanation, the examiner's original—and ultimately reversed—rejection, which spanned one-hundred pages" and "did not adduce expert testimony or even present attorney argument on why one of skill would have been motivated to combine … the [] prior art references." *Id*. at 975-76. Similarly, Exelixis cites to *Intendis GMBH v. Glenmark Pharms. Ltd.* for the position that this Court has rejected "bucket-based motivation to combine arguments." 117 F. Supp. 3d 549, 590-91 (D. Del. 2015). In that case, however, the defendant in its post-trial briefing raised a combination for the first time and "urge[d] the court to consider the combination of two 'buckets' of references" that defendant's expert "never testified as to" and would have required the court to "speculat[e]" "without guiding testimony or evidence" as to the motivation to combine. *Id*. And in *Motorola Mobility, LLC v. Int'l Trade Comm'n*, the accused

infringer "did not clearly identify the scope and content of the prior art" and did not "provide any argument that certain prior art references render a specific claim obvious," but simply relied on statements from the patentee's expert about the prior art discussed in the patent. 737 F.3d 1345, 1350 (Fed. Cir. 2013). As discussed above, the reports submitted by Drs. Lepore and Steed disclose specific combinations, specific motivations, and specific expectations of success. Further, in none of these three cases did the court exclude any opinions or testimony under *Daubert*, but rather only found that the defendant "did not prove" its burden. *Id*.; *see also ProBatter,* 680 F. App'x at 975 (defendant did not "meet its burden of proving invalidity."); *Intendis,* 117 F. Supp. 3d 591 (the evidence "cannot satisfy defendants' burden.").

Regarding identifying specific combinations, Exelixis relies on *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.* where the court did not exclude testimony under *Daubert*, but found the testimony on combinations to be conclusory where there was "no relation to any specific combination of prior art elements . . . from specific references," 694 F.3d 1312, 1327 (Fed. Cir. 2012). There, however, the court took issue with the testimony because the expert merely stated that "[t]he motivation to combine would be because you wanted to build something better," which the court considered "generic." *Id*. In *Innogenetics, NV v. Abbott Laboratories*, "[t]here was a complete absence of any proof" of a motivation to combine "based upon [the expert]'s list of prior art references or the knowledge generally available to those of ordinary skill in the art for *any* reason." 512 F. 3d 1363, 1373 n.3 (Fed. Cir. 2008) (emphasis in original). Further, in *Oxford Gene Tech. Ltd. v. Mergen Ltd.*, the expert's report was "devoid of factual support" and the expert "did not provide any basis for his conclusion" and the court concluded that the patentee could not "be expected to cross-examine [the expert] regarding the methodology he used to reach [his] conclusion when he could not or would not disclose the factual evidence upon which he

relied." 345 F. Supp. 2d 431, 437-438, 440-441 (D. Del. 2004). And in *Asahi Glass Co., Ltd. v. Guardian Indus. Corp.*, the expert "d[id] not describe the state or skill in the art" and did not construe the meaning of a disputed claim limitation. 2011 WL 4459606, at *2 (D. Del. Sept. 26, 2011). Unlike the authority relied upon by Exelixis, Drs. Lepore and Steed disclosed specific combinations of prior art with detailed factual support.

The authority cited by Exelixis that conclusory statements cannot support a motivation to combine or reasonable expectation of success are also readily distinguishable. In *TQ Delta, LLC v. CISCO Sys.,* the expert "offer[ed] only unsupported and conclusory statements" regarding the motivation to combine and "fail[ed] to identify any other evidence." 942 F.3d 1352, 1362 (Fed. Cir. 2019). In *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, the court did *not* find that enhanced bioavailability is not a sufficient motivation to combine, as Exelixis claims. 913 F.3d 1076, 1087 (Fed. Cir. 2019). Rather, the court stated that it "may be true in some cases" that bioavailability is a sufficient motivation, but "that [the patentee's expert] better addressed the bioavailability issue" to conclude that the compound "did not demonstrate a bioavailability problem." *Id*. And in *ZF Meritor, LLC v. Eaton Corp.*, the Third Circuit found that the district court abused its discretion in not permitting the expert testimony because the testimony concerned issues that "the parties envisioned all along" and therefore "it c[ould] not seriously be a surprise to any of the parties." 696 F.3d 254, 298 (3d Cir. 2012). As discussed above, Drs. Lepore and Steed submitted detailed motivations to combine with reasonable expectations of success.

F. Drs. Lepore and Steed Did Not Rely On the Inventor's Path.

As Exelixis concedes, "Dr. Lepore and Dr. Steed insist that their obviousness opinions are not based on [] inventor testimony or Exelixis' development path." (Br. at 12.) Exelixis contends, however, that their discussions of inventor testimony and Exelixis' development should nevertheless be thrown out because considering that evidence would be "contrary to established

law." *Id*. This Court, however, has found that evidence that is "not statutory prior-art" "c[an] be used to show the state of the art" where that evidence describes work that "began before the priority date." *In re Copaxone Consol. Cases*, No. CV 14-1171-GMS, 2017 WL 401943, at *14 (D. Del. Jan. 30, 2017), *aff'd sub nom*. *In Re: Copaxone Consol. Cases*, 906 F.3d 1013 (Fed. Cir. 2018).

The evidence described in Dr. Steed's report primarily concerns [redacted] (Steed Opening Report at ¶ 274; *see also* ¶¶ 267-284.) Dr. Steed also discusses [redacted] (*Id*. at ¶ 293; *see also* ¶¶ 282-297.) Exelixis internal documents and witness testimony demonstrate that Exelixis was merely practicing the prior art. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 1367 ("[C]onsideration of the 'routine testing' performed by Pfizer is appropriate.")

Similarly, in Dr. Lepore's Report, he cites to testimony from the inventors discussing the prior art (Lepore Opening Report at ¶¶ 301-302) or specifically commenting on Dr. Lepore's motivations to combine (*id*. at ¶¶ 303-304, 308-311) or expectations of success (*id*. at ¶¶ 305-307). Such testimony, although not prior art, can be "properly used as indicators of the level of ordinary skill in the art to which the invention pertained." *Thomas & Betts Corp. v. Litton Sys., Inc*., 720 F.2d 1572, 1580-81 (Fed. Cir. 1983); *see also In re Wilson*, 311 F.2d 266, 268-69 (C.C.P.A. 1962) (approving citation to document that was not prior art to show a fact about the prior art).

G. Commercial Motivations Are Properly Considered in An Obviousness Analysis.

Exelixis claims, without citation, that Dr. Lepore's "reli[ance] on commercial motivations as part of his obviousness opinions … is contrary to Federal Circuit law." (Br. at 12-13.) It is Exelixis' argument, however, that is contrary to Supreme Court law, because "[i]t is well-established" that "market pressure to solve a problem" and the fact that "market forces can prompt variations of [a design]" can be considered under *KSR*. *KSR*, 550 U.S. at 418, 421; *In re Copaxone*, 2017 WL 401943, at *12. Exelixis' claim that "scientific motivations pointed in the other direction," (*id.* at 12), is wrong factually and, even if true, would not compel exclusion of commercial motivations. *KSR*, 550 U.S. at 419 ("The diversity of inventive pursuits and of modern technology counsels against limiting the analysis … it often may be the case that market demand, rather than scientific literature, will drive design trends.").

IV. CONCLUSION

MSN respectfully requests that the Court deny Exelixis' Motion To Exclude the Obviousness Opinions of Dr. Lepore and Dr. Steed and Any Reference to Them By Other Experts.

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